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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/424,244	04/11/00	STRAUSS	A P64075US0

000136
JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON DC 20004

HM12/0726

EXAMINER	
HINES, I	
ART UNIT	**PAPER NUMBER**
1645	7

DATE MAILED: 07/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/424,244	Strauss et al.
Examiner	**Art Unit**
Ja-Na Hines	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 9, 1999*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Specification

1. The use of the trademark TRITON-X ™ and other diagnostics and reagents have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps in claim 1 are: no detection step and no correlation step. The term assaying the enzymatic activity does not teach detection, and there is no correlation step between assaying the enzymatic activity and identifying active substances which affect covalent bonding.

3. Regarding claim 3, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MEP. § 2173.05(d).

4. Claims 6-7 and 9 are rejected. Claims 6 and 9 recite the sequence LPXTG, without reciting the sequence identifying number. The sequence must be identified with a sequence identifying number.

5. Claim 12 is rejected. Acronyms like Lif must be spelled out when used for the first time in a chain of claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-2, 5, 9-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Samuelson (J. Bact., 1995). Samuelson (J. Bact., 1995) teaches cell surface display of recombinant proteins on *Staphylococcus carnosus*. Surface display of heterologous proteins on bacterial cells is an important objective for many applications in microbiology and molecular biology (page 1470). The use of enzyme-coated bacteria as novel biocatalyst has been envisioned because enzymes with retained activity have been surface displayed on *E.coli* cells (page 1470). Investigations with gram positive bacteria for cell surface display of has been initiated (page 1470). The surface receptors of gram positive bacteria seem to be more permissive for the insertion of extended sequences of foreign proteins then do the different gram-negative systems

(page 1470). Gram-positive bacteria have the additional advantage of being more rigid because of the thicker cell wall, thus making it possible to use the intact bacteria for separation purposes (page 1470). A 198 amino acid region, designated ABP (albumin binding protein) was expressed adjacent to the cell wall to increase accessibility to the surface-displayed target peptides (page 1471). The Materials and Methods section teaches enzymatic assay for the detection of recombinant surface displayed receptors (page 1471) and immunofluorescence assay for detection of peptides on the cell surface (page 1472). The method teaches contacting the sample and using a fluorescence activated cell sorter to analysis the bacteria (page 1472). The colorimetric assay for detection used strep avidin-alkaline phosphatase to detect a color change (page 1473). Recombinant and wild-type *S.carnosus* cells were grown and subjected to the enzymatic assay, performed in an ELISA plate format, wherein a positive color response was found for the cultivation harboring plasmids (page 1473). See Figure 3 which compares the wild type to the cultivations harboring plasmids. This demonstrates that hybrid receptors with serum albumin binding capacity were accessible on the cell surface (page 1474). For cell surface binding, anchoring regions were investigated (page 1475). There is a charged repetitive region postulated to interact with the peptidoglycan cell wall and a region common for gram-positive cell surface bound receptors containing an LPXTGX motif, a C-terminal hydrophobic region and a charged tail (page 1475). It has been demonstrated that all three regions are required for cell surface anchoring and that the cell sorting is accompanied by proteolytic cleavage at the C-terminus and covalent linking of the surface receptor to the cell wall (page 1475). Finally, flow cytometry was

successfully employed and a fluorescence-labeled secondary antibody and a primary antibody reactive with the ABP region of the hybrid receptors could be used to stain the cells (page 1475).

Therefore, Samuelson (J. Bact., 1995) teaches a method for identifying active substances on the surface of gram-positive bacteria.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 3-4, 6, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995). Samuelson (J. Bact., 1995) has been discussed however, Samuelson (J. Bact., 1995) does not teach the cell wall structure and hybrids polypeptide succession. Schneewind (Science, 1995) teaches structure of the cell wall anchor of surface proteins in *Staphylococcus aureus*. Many surface proteins are anchored to the cell wall of gram-positive bacteria and are involved in the pathogenesis of these organisms (abstract). A hybrid molecule was designed and when expressed is anchored to the cell wall and can be released by controlled enzymatic digestion (abstract). By a combination of molecular biology and mass spectroscopy techniques, the structure of the cell wall anchor of surface proteins was revealed (abstract). After cleavage of surface proteins between threonine and glycine of the

conserved LPXTG motif, the carboxyl of threonine is amide linked to the free amino group of the pentaglycine cross bridge in the staphylococcal cell wall (abstract). The N-terminal immunoglobulin-binding domains of protein A are displayed on the cell surface, whereas the C-terminal end is anchored to the bacterial cell wall (page 103). This ability to anchor to the cell wall requires a 35 residue sorting signal that is located at the predicted C-terminus of protein A and consists of an LPXTG motif, followed by a C-terminal hydrophobic domain and a tail of mostly positively charged residues (page 103). Cell wall anchored molecules of gram positive bacteria have similar topologies in that the N-terminal domain is displayed on the cell surface, whereas the C-terminal anchor structure is buried in the thick peptidoglycan layer (page 103). The pentaglycine peptide, lysostaphin cleaves randomly between any of the four glycyl-glycine peptide bonds (page 105). The lysostaphin cleavage occurred between the third and fourth glycine of the pentaglycine cross bridge, s selectivity which could be the result of the stearic hindrance imposed by the anchored protein and the linked cell wall peptide (page 105). Surface proteins are exported by a means of an N-terminal signal/leader sequence (page 105), See figure 4A and 4B. The release of peptidoglycan fragments with linked surface proteins in gram-positive bacteria may be caused by physiological turnover and the enzyme responsible may represent a novel target for antibacterial therapy (page 105).

Therefore, it would have been obvious at the time of applicants invention to have used the method of Samuelson (J. Bact., 1995) with polypeptides which effect the cell wall, pathogenicity, use linker peptides and teach cell wall exchange as taught by Schneewind (Science, 1995),

because Schneewind (Science, 1995) teaches the structure of the cell wall anchor of surface proteins and designed an expressed hybrid molecule.

8. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995) in further view of Strauss et al. Samuelson (J. Bact., 1995) has been discussed however, Samuelson (J. Bact., 1995) does not teach the enzyme being a proenzyme. Strauss et al., teaches in vivo immobilization of enzymatically active polypeptides on the cell surface of *Staphylococcus carnosus*. Many surface proteins of gram-positive bacteria are covalently anchored to the cell wall by ubiquitous mechanisms, involving a specific, C-terminal sorting signal (abstract). To achieve cell wall immobilization of a normally secreted enzyme in vivo, the authors constructed a hybrid protein consisting of *Staphylococcus hyicus* lipase and *S.aureus* fibronectin binding protein B (abstract). The lipase is a pre-proenzyme (page 492). Expression of the hybrid protein in *S.carnosus* resulted in efficient cell-wall anchoring of enzymatically active lipases (abstract). The cell wall lipase retained more than 80% of the specific activity as compared to unmodified lipase (abstract). When the lipase was replaced by another enzyme, the resulting hybrid was also efficiently anchored in an active conformation to the cell wall of the bacteria (abstract). The results demonstrate that it is possible to immobilize normally soluble enzymes on the cell wall of *S.carnosus*, without radically altering their catalytic activity, by fusing them to a cell wall

immobilization unit, consisting of a suitable cell wall spanning region and a standard cell wall sorting signal (abstract).

Accordingly, it would have been obvious at the time of applicants invention to have used proenzymes as taught by Strauss et al., in the method of identification as taught by Samuelson (J. Bact., 1995) in view of Schneewind (Science, 1995), because Strauss et al., teaches that proenzymes are usable with the well known method of identifying substances which affect the covalent bonding of polypeptides to the surface of gram-positive bacteria.

Sequence Compliance

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures because the specification and claims recite an amino acid sequence with the designated sequence number identifier.

APPLICANT IS GIVEN A THE TIME SET FORTH IN THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by

the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Prior Art

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Brito et al., teaches purification and peptidase activity of a bacteriolytic enzyme. Schneewind et al., (1992) teaches sorting of protein A to the Staphylococcal cell wall.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

July 23, 2001

7/23/01

JENNIFER E. GRASER
PRIMARY EXAMINER